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(54) **Novel orally-active elastase inhibitors.**

(57) This invention relates to novel morpholinourea and related derivatives of pentafluoroethyl peptides which are orally active elastase inhibitors. Pharmaceutical compositions containing these compounds are useful in the treatment of various inflammatory diseases and emphysema.

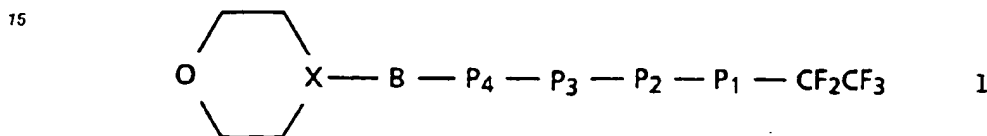
**EP 0 529 568 A1**

This invention relates to orally-active elastase inhibitors and pharmaceutical compositions containing them.

In its broad aspects, this invention relates to analogs of peptidase substrates in which the carboxy terminal carboxyl group has been replaced by a pentafluoroethylcarbonyl (-C(O)C<sub>2</sub>F<sub>5</sub>) group and in which the amino terminal amino acid is protected by various heterocycle-containing groups such as a 4-morpholinecarbonyl group. These elastase inhibitors exert valuable pharmacological activities and therefore pharmaceutical compositions containing them have useful physiological consequences in a variety of disease states.

In its more specific aspects, this invention relates pentafluoroethylcarbonyl analogs of certain elastase substrates which have various heterocyclic containing protecting groups which are useful in inhibiting elastase, the inhibition of which will have useful physiological consequences in a variety of disease states.

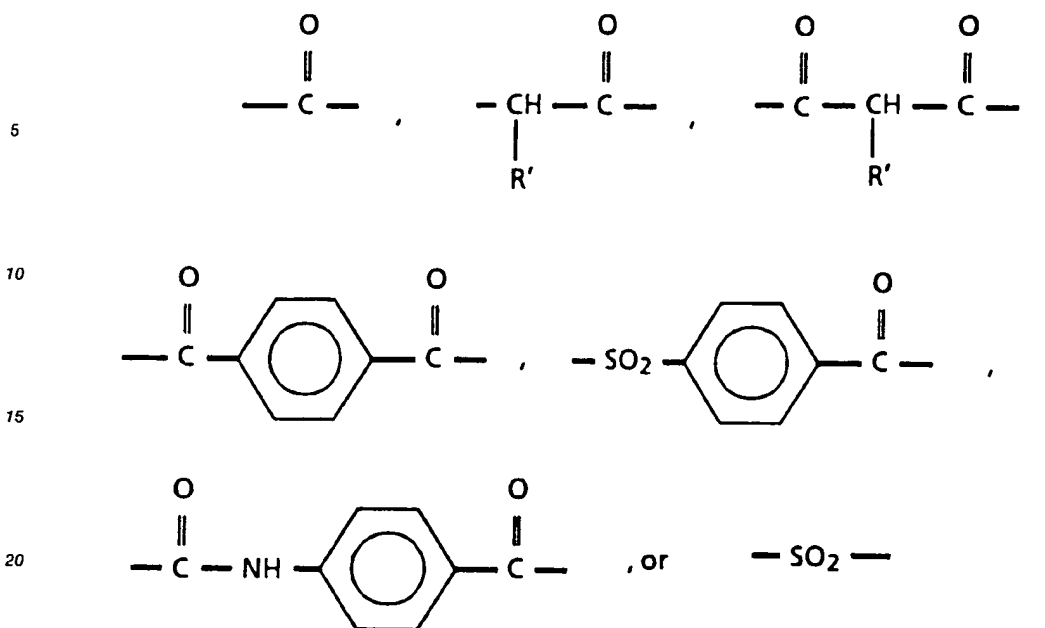
The contemplated elastase inhibitors are selected from the generic formula



# SEQ. ID 1

25 wherein

- P<sub>1</sub> is Ala, bAla, Leu, Ile, Val, Nva, bVal, Met, Nle, Gly, or an N-methyl derivative;
- P<sub>2</sub> is Ala, bAla, Leu, Ile, Val, Nva, bVal, Met, Nle, Gly, Phe, Tyr, Trp, or Nal(1) where the nitrogen of the alpha-amino group can be substituted with an R group where R is a (C<sub>1-6</sub>)alkyl, (C<sub>3-12</sub>)cycloalkyl, (C<sub>3-12</sub>)cycloalkyl(C<sub>1-6</sub>)alkyl, (C<sub>4-11</sub>)bicycloalkyl, (C<sub>4-11</sub>)bicycloalkyl(C<sub>1-6</sub>)alkyl, (C<sub>6-10</sub>)aryl, (C<sub>6-10</sub>)aryl(C<sub>1-6</sub>)alkyl, (C<sub>3-7</sub>)heterocycloalkyl, (C<sub>3-7</sub>)heterocycloalkyl(C<sub>1-6</sub>)alkyl, (C<sub>5-9</sub>)heteroaryl, (C<sub>5-9</sub>)heteroaryl(C<sub>1-6</sub>)alkyl, fused (C<sub>6-10</sub>)aryl(C<sub>3-12</sub>)cycloalkyl, fused (C<sub>6-10</sub>)aryl(C<sub>3-12</sub>)cycloalkyl(C<sub>1-6</sub>)alkyl, fused (C<sub>5-9</sub>)heteroaryl(C<sub>3-12</sub>)cycloalkyl, or fused (C<sub>5-9</sub>)heteroaryl(C<sub>3-12</sub>)cycloalkyl(C<sub>1-6</sub>)alkyl, or P<sub>2</sub> is Pro, 1,2,3,4-tetrahydro-3-isoquinoline carboxylic acid (Tic), thiazolidine-4-carboxylic acid (Tca), or Ind;
- 35 P<sub>3</sub> is Ala, bAla, Leu, Ile, Val, Nva, bVal, Met, or Nle or an N-methyl derivative, Pro, Ind, Tic or Tca, Lys or Orn each substituted on its omega amino group with a morpholino-B-group;
- P<sub>4</sub> is Ala, bAla, Leu, Ile, Val, Nva, bVal, Met, or Nle or an N-methyl derivative or a bond; and
- B is a group of the formulae



25 R' is a hydrogen or a C<sub>1-6</sub> branched or straight chain alkyl group;  
X is N or CH;

or a hydrate, isostere, or pharmaceutically acceptable salt thereof.

Isosteres of the compounds of formula 1 include those wherein (a) one or more of the  $\alpha$ -amino residues of the P<sub>1</sub>-P<sub>4</sub> substituents are in its unnatural configuration (when there is a natural configuration) or (b) when the normal peptidic amide linkage is modified, such as for example, to form -CH<sub>2</sub>NH- (reduced), -COCH<sub>2</sub>- (keto), -CH(OH)CH<sub>2</sub>- (hydroxy), -CH(NH<sub>2</sub>)CH<sub>2</sub>- (amino), -CH<sub>2</sub>CH<sub>2</sub>- (hydrocarbon), -CH=CH- (alkene). Preferably a compound of the invention should not be in an isosteric form; particularly it is preferred that there be no modified peptidic amide group, but if there is, it is preferable to keep the isosteric modifications to a minimum. Of course, it is also understood that in those instances wherein the carbonyl moiety of P<sub>1</sub> is in its reduced form, then such compounds are not hydrates.

As used herein the term "(C<sub>1-6</sub>)alkyl" means a straight or branched alkyl group of from 1 to 6 carbon atoms, such as, methyl, ethyl, n-propyl, isopropyl, n-butyl, tert-butyl, n-pentyl, sec-pentyl, iso-pentyl, and n-hexyl. The term "(C<sub>3-12</sub>)cycloalkyl" means a cyclic alkyl group consisting of a 3 to 8 member ring which can be substituted by a lower alkyl group, for example, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, 4-methylcyclohexyl, 4-ethylcyclohexyl, cycloheptyl, and cyclooctyl. The term "(C<sub>3-12</sub>)cycloalkyl(C<sub>1-6</sub>)alkyl" means a (C<sub>1-6</sub>)alkyl group substituted by a (C<sub>3-12</sub>)cycloalkyl group, such as a cyclohexylmethyl or cyclopentylethyl group. The term "(C<sub>4-11</sub>)bicycloalkyl" means an alkyl group containing one pair of bridgehead carbon atoms, such as 2-bicyclo[1.1.0]butyl, 2-bicyclo[2.2.1]hexyl, and 1-bicyclo[2.2.2]octane. The term "(C<sub>4-11</sub>)bicycloalkyl(C<sub>1-6</sub>)alkyl" means a (C<sub>1-6</sub>)alkyl substituted by a (C<sub>4-11</sub>)bicycloalkyl, such as 2-bicyclohexylmethyl. The term "(C<sub>6-10</sub>)aryl" means a cyclic, aromatic assemblage of conjugated carbon atoms, for example, phenyl, 1-naphthyl, and 2-naphthyl. The term "(C<sub>6-10</sub>)aryl(C<sub>1-6</sub>)alkyl" means a (C<sub>1-6</sub>)alkyl substituted by a (C<sub>6-10</sub>)aryl, such as benzyl, phenethyl, and 1-naphthylmethyl. The term "-(C<sub>3-7</sub>)heterocycloalkyl" means a nonaromatic, carbon containing cyclic group which contains from 1 to 3 heteroatoms selected from oxygen, nitrogen and sulfur, such as morpholinyl and piperidinyl. The term "-(C<sub>3-7</sub>)heterocycloalkyl(C<sub>1-6</sub>)alkyl" means a (C<sub>1-6</sub>)alkyl group substituted by a (C<sub>3-7</sub>)heterocycloalkyl group, for example, morpholinomethyl. The term "(C<sub>5-9</sub>)heteroaryl" means a cyclic or bicyclic, aromatic assemblage of conjugated carbon atoms and from 1 to 3 nitrogen, oxygen, and sulfur atoms, for example, pyridinyl, 2-quinoxaliny, and quinolinyl. The term "(C<sub>5-9</sub>)heteroaryl(C<sub>1-6</sub>)alkyl" means (C<sub>1-6</sub>)alkyl group substituted by a (C<sub>5-9</sub>)heteroaryl group, such as, 3-quinolinylmethyl. The term "fused (C<sub>6-10</sub>)aryl(C<sub>3-12</sub>)cycloalkyl" means a "(C<sub>3-12</sub>)cycloalkyl" group which has one or more sides shared with a "(C<sub>6-10</sub>)aryl" group and can, for example, include groups derived by the fusion of benzene and cyclopentane, that is 2-indanyl. The term "fused (C<sub>6-10</sub>)aryl(C<sub>3-12</sub>)cycloalkyl(C<sub>1-6</sub>)alkyl" means a (C<sub>1-6</sub>)alkyl substituted by a fused (C<sub>6-10</sub>)aryl(C<sub>3-12</sub>)cycloalkyl group. The term "fused (C<sub>5-9</sub>)heteroaryl(C<sub>3-8</sub>)cycloalkyl" means a

(C<sub>5-9</sub>)heteroaryl group which has one or more sides shared with a (C<sub>3-8</sub>)cycloalkyl group and can, for example, include groups derived by the fusion of cyclohexane and pyridine, that is tetrahydroquinoline. Finally the term "fused (C<sub>5-9</sub>)heteroaryl(C<sub>3-8</sub>)cycloalkyl(C<sub>1-6</sub>)alkyl" means a (C<sub>1-6</sub>)alkyl substituted by a fused (C<sub>5-9</sub>)heteroaryl(C<sub>3-8</sub>)cycloalkyl group.

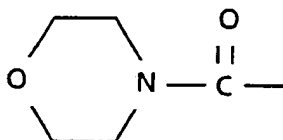
Unless otherwise stated, the  $\alpha$ -amino acids of these peptidase substrate analogs are preferably in their L-configuration; however, the amino acids of the formula 1 compounds can be of either the D- or L-configurations or can be mixtures of the D- and L-isomers, including the racemic mixture. Also, the carbon adjacent to the carboxy terminal -C(=O)CF<sub>2</sub>CF<sub>3</sub> moiety can also be the D- or the L-optical isomer and can also be a mixture of such isomers. The recognized abbreviations for the  $\alpha$ -amino acids are set forth in Table

I.

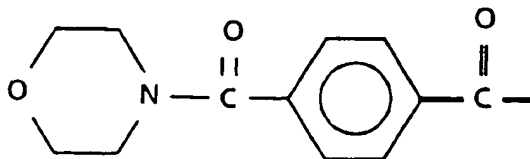
TABLE I

AMINO ACID	SYMBOL
Alanine	Ala
Glycine	Gly
Isoleucine	Ile
Leucine	Leu
Lysine	Lys
Phenylalanine	Phe
Proline	Pro
Tryptophan	Trp
Tyrosine	Tyr
Valine	Val
Norvaline	Nva
Norleucine	Nle
1-Naphthylalanine	Nal(1)
2-Indolinecarboxylic acid	Ind
Sarcosine	Sar
beta-Alanine	bAla
beta-Valine	bVal
Methionine	Met
1,2,3,4-Tetrahydro-3-isoquinoline carboxylic acid	Tic
Thiazolidine-4-carboxylic acid	Tca
Ornithine	Orn

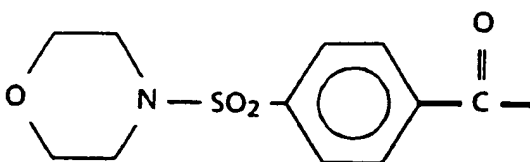
Some of the preferred compounds of this invention are also morpholino urea derivatives by virtue of the fact that the amino terminal amino group of the peptide chain is protected by a 4-morpholinecarbonyl group. The 4-morpholinecarbonyl protecting group of the formula



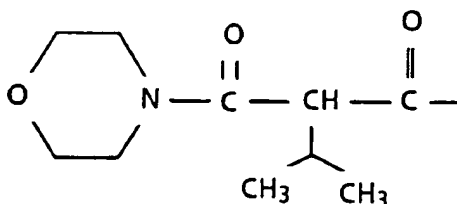
is abbreviated throughout as MC. Other preferred compounds of this invention are 4-morpholinecarbonyl-benzoyl, abbreviated throughout as MCBz, derivatives wherein the morpholine-B group is of the formula



Yet other preferred compounds of this invention are 4-morpholine sulfonylbenzoyl derivatives wherein the morpholine-B group is of the formula



Still other preferred compounds of this invention are 2-(N-morpholinocarbonyl)-3-methyl-butanoyl derivatives wherein the morpholine-B group is of the formula



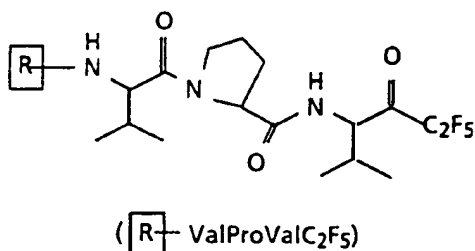
Of the compounds of formula 1 applicants also prefer those compounds wherein P<sub>1</sub> is norvaline or valine. Also preferred are those formula 1 compounds wherein P<sub>2</sub> is a proline or glycine; wherein P<sub>3</sub> is isoleucine, valine, or alanine; and wherein P<sub>4</sub> is alanine or is a bond. Other preferred compounds of formula 1 are those wherein alpha amino group of the P<sub>2</sub> group is substituted by an R group, especially those wherein the R group is a methyl group or a 2-indanyl group. Specifically preferred compounds of formula 1 are:

40                   MC-Ala-Ala-Pro-Val-C<sub>2</sub>F<sub>5</sub>,                   SEQ. ID 2  
                       MC-Val-Pro-Val-C<sub>2</sub>F<sub>5</sub>,  
                       MCBZ-Ala-Ala-Pro-Val-C<sub>2</sub>F<sub>5</sub>, and                   SEQ. ID 3  
 45                   MCBZ-Val-Pro-Val-C<sub>2</sub>F<sub>5</sub>.

Human leukocyte elastase is released by polymorphonuclear leukocytes at sites of inflammation and thus is a contributing cause for a number of disease states. Thus pharmaceutical compositions containing the peptidase substrates of formula 1 have an anti-inflammatory effect useful in the treatment of gout, rheumatoid arthritis and other inflammatory diseases, such as adult respiratory distress syndrome, septicemia, and disseminated intravascular coagulation, cystic fibrosis, and in the treatment of emphysema. In their end-use application the enzyme inhibitory properties of the compounds of formula 1 are readily ascertained by standard biochemical techniques well known in the art. Potential dose range for their end-use application will of course depend upon the nature and severity of the disease state as determined by the attending diagnostician with the range of 0.01 to 200 mg/kg body weight per day being useful for the aforementioned disease states with 0.1 mg to 50 mg/kg per day being preferred.

Human elastase is assayed *in vitro* using chromophoric peptides, succinylalanylalanylalanyl-p-nitroanilide, methoxysuccinylalanylalanylprolylvalyl-p-nitroanilide, and others, all of which are available commercially. The assay buffer, pH 8.0, and assay techniques are similar to those described by R. Lottenberg, et al., *Biochimica et Biophysica Acta*, 742, pp. 539-557 (1983). Enzyme is purified from human sputum, although recently it has become commercially available. Kinetic characterization of immediate inhibitors is by means of the Dixon plot, whereas the characterization of slow- and/or tight-binding inhibitors used data analysis techniques reviewed by Williams and Morrison. The synthesis and analytical use of a highly sensitive and convenient substrate of elastase is described in J. Bieth, B. Spiess and C.G. Wermuth, *Biochemical Medicine*, 11 (1974) 350-375. Table 1 summarizes the ability of selected compounds of this invention and a compound of the prior art to inhibit elastase. Table 2 summarizes the oral activity of various compounds when evaluated in the elastase-induced hemorrhage model in hamster.

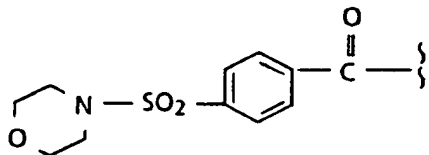
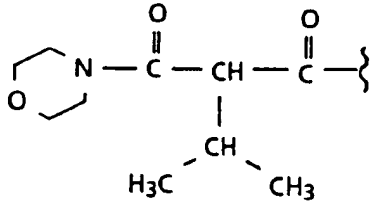
TABLE 2



MDL #	R	K <sub>i</sub> (nM)*
101,146		20
102,823		60
100,948A	 •HCl	60
102,111		170
101,773		261

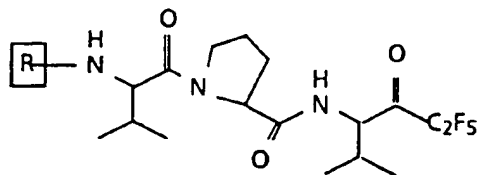
\* for human neutrophil elastase, using N-MeOSucAlaAlaProVal-pNA as substrate

TABLE 2 (continued)

<u>MDL #</u>	<u>R</u>	<u>K<sub>i</sub> (nM)*</u>
101,788		2.36
100,050		44

\* for human neutrophil elastase, using N-MeOSucAlaAlaProVal-pNA as substrate

TABLE 3  
SUMMARY OF ORALLY ACTIVE ELASTASE INHIBITORS



MDL Number	R	K <sub>i</sub> (nM)	Oral Activity	
			Dose	% Inhibition
102,111		170	100 mg/Kg 50 mg/Kg 25 mg/Kg 10 mg/Kg	79* 70* 61* 30
100,948A		60	50 mg/Kg 10 mg/Kg	77* 39
101,230		70	25 mg/Kg 10 mg/Kg	41 0
101,146		20	50 mg/Kg 25 mg/Kg 10 mg/Kg	74* 56* 25
100,867		43	50 mg/Kg 10 mg/Kg	26 0

\* means significant at  $P < .05$

In general, the compounds of formula I may be prepared using standard chemical reactions analogously known in the art. The procedure for preparing the formula I compounds wherein B is -CO- is outlined in Scheme A wherein P<sub>1</sub>, P<sub>2</sub>, P<sub>3</sub>, and P<sub>4</sub> are as previously defined or are functional equivalents of these groups and Pg is an amino protecting group such as a carbamate, preferably a t-butyloxycarbonyl (Boc) group. The compounds of Formula I wherein B is other than -CO- can be prepared analogously, merely by substituting the appropriate intermediate, which can be the corresponding acid or sulphonyl chloride or the acid for the compound of formula 6 in Scheme A.



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hours, depending on the reactants, the solvent, the concentrations, and other factors, such as the temperature which can be from about 0°C to about 60°C, conveniently at about room temperature, i.e. 25°C. The formula 1 product can be isolated from the reaction mixture by any appropriate techniques such as by chromatography on silica gel eluting with, for example, a mixture of acetone and ethyl acetate.

5 The formula 5 pentafluoroethyl peptide can be prepared by, for example, protecting group removal from the corresponding formula 4 pentafluoroethyl peptide which is in turn prepared by the reaction of the formula 2 di- or tri-peptide and the pentafluoroethyl derivative of the P<sub>1</sub> amino acid, 3. The reaction of the formula 2 di- or tri-peptide with the formula 3 compound can be promoted by procedures known to promote peptide amide bond formation, such as by reacting the formula 2 di- or tri-peptide with isobutyl chloroformate ("IBCF") preferably in the presence of a HCl acceptor such as mentioned above, preferably NMM, and then adding the formula 3 compound. The reaction of the formula 2 peptide with IBCF is performed by, for example, adding about an equimolar amount of IBCF to a cooled (-10 to -20°C) solution of the formula 2 peptide and up to about 5 molar equivalents of NMM. After a short time (15 minutes to several hours), the formula 3 peptide is added and the reaction is allowed to proceed for from about 30 minutes to about 10 hours depending on the reactants, the solvent and concentration of reactants. After this initial reaction period the reaction is allowed to warm to room temperature. The product is isolated in any convenient manner such as by washing the reaction mixture with acid, mild base solution such as dilute sodium bicarbonate solution, and brine, and subsequently drying the organic phase and subsequently by evaporation of any solvent. Solvents for this reaction can be any convenient and appropriate solvent such as those mentioned above and preferably will be methylene chloride or a methylene chloride/acetonitrile mixture.

The protecting group is removed from the formula 4 compound in any appropriate manner and the procedure will, of course, depend on the nature of the protecting group and the nature of any other reactive groups on the compound. For example, when the protecting group is a t-butyloxycarbonyl (Boc) group, the formula 4 compound can be converted to the formula 5 compound salt by treatment with gaseous hydrogen chloride in ethyl acetate. When the protecting group is a carbobenzyloxy (Cbz) group, the formula 4 compound can be converted to the formula 5 compound by catalytic hydrogenation.

The formula 2 peptide is prepared by sequentially coupling the requisite amino acids using conventional techniques. In some instances the required di- and tri-peptides are commercially available.

In coupling individual amino acids or peptides, appropriate side chain protecting groups are employed. The selection and use of an appropriate protecting group for these side chain functionalities is within the ability of those skilled in the art and will depend upon the amino acid to be protected and the presence of other protected amino acid residues in the peptide. The selection of such a side chain protecting group is critical in that it must not be removed during the deprotection and coupling steps of the synthesis. For example, when Boc is used as the α-amino protecting group, the following side chain protecting groups are suitable: p-toluenesulfonyl (tosyl) moieties can be used to protect the amino side chains of amino acids such as Lys; and a 2-bromocarbobenzyloxy (2Br-Z) moiety can be used to protect the hydroxy containing side chains of amino acids such as Tyr. These side chain protecting groups are added and removed according to standard practices and procedures well known in the art. It is preferred to deprotect these side chain protecting groups with a solution of anisole in anhydrous hydrogen fluoride (1:10). Typically, deprotection of side chain protecting groups is performed after the peptide chain synthesis is complete but these groups can alternatively be removed at any other appropriate time. It is preferred to deprotect these side chains at the same time as the peptide is cleaved from the resin when solid phase synthetic methods are employed.

The formula 3 pentafluoroethyl derivative of the P<sub>1</sub> amino acid can be prepared as described in European Patent Application Serial Number 90114250, published January 30, 1991.

The compounds are then isolated and purified by standard techniques. The desired amino acids, derivatives and isomers thereof can be obtained commercially or can be synthesized according to standard practices and procedures well known in the art.

The following specific examples are given to illustrate the preparation of various compounds of this invention although the scope of the invention is not meant to be limited to the compounds exemplified below.

**EXAMPLE 1****Preparation of MC-Val-Pro-Val-CF<sub>2</sub>CF<sub>3</sub>**5 a) **Preparation of Boc-Val-Pro-Val-CF<sub>2</sub>CF<sub>3</sub>**

To a stirred solution of Boc-Val-Pro-OH (1.10 g, 3.5 mmole) in CH<sub>2</sub>Cl<sub>2</sub> (20 ml) under argon, cooled to -17 °C, was added NMM (0.40 ml, 3.68 mmole). After 5 minutes, 1 equivalent (0.45 ml, 3.5 mmole) of IBCF was added and a light suspension formed several minutes later. After 20 minutes NMM (0.4 ml, 3.68 mmol) was added followed by a suspension of H-Val-CF<sub>2</sub>CF<sub>3</sub>·HCl (0.88 g, 3.50 mol) in CH<sub>2</sub>Cl<sub>2</sub> (10 ml) plus CH<sub>3</sub>CN (10 ml) dropwise (from an addition funnel) over ca. 15 minutes. The reaction was stirred at -14 to -18 °C for 1 hour and then the cooling bath was removed. The reaction was allowed to warm to room temperature (ca. 40 min.) and diluted with CH<sub>2</sub>Cl<sub>2</sub> (100 ml). The organic phase was washed with 1 N HCl (3 x 75 ml), satd. NaHCO<sub>3</sub> (2 x 75 ml), and brine (50 ml). Drying (Na<sub>2</sub>SO<sub>4</sub>) and concentration gave a colorless oil which was placed under high vacuum to give the desired product as a white foam (1.59 g, 88%). Elemental analysis; calculated for C<sub>22</sub>H<sub>34</sub>F<sub>5</sub>N<sub>3</sub>O<sub>5</sub>: %C = 51.26, %H = 6.65; %N = 8.15. Found: %C = 50.80, %H = 6.57, %N = 7.85.

20 b) **Preparation of H-Val-Pro-Val-CF<sub>2</sub>CF<sub>3</sub>·HCl**

Into a stirred solution of the product of part (a) (1.52 g, 2.95 mmole) in ethyl acetate (75 ml) cooled in an ice-water bath was bubbled HCl gas for 10 minutes, after which the reaction flask was capped with a septum. TLC after 1 hour indicated the absence of starting material. The reaction mixture was concentrated, the residue dissolved in ethyl acetate and concentrated (2 x) to give a white solid which was dried under high vacuum over KOH pellets. Dried weight was 1.35 g. Elemental Analysis; Calcd for C<sub>17</sub>H<sub>26</sub>F<sub>5</sub>N<sub>3</sub>O<sub>3</sub>·HCl: %C = 45.19, %H = 6.02; %N = 9.30. Found: %C = 44.84, %H = 6.22; %N = 8.88. High resolution mass spectrum calcd for C<sub>17</sub>H<sub>27</sub>F<sub>5</sub>N<sub>3</sub>O<sub>3</sub> (MH<sup>+</sup>) = 416.1973, found MH<sup>+</sup> = 416.1972, error = -0.2 ppm.

30 c) **Preparation of MC-Val-Pro-Val-CF<sub>2</sub>CF<sub>3</sub>**

To a stirred solution of the product of part (b) (1.06 g, 2.35 mmole) in CH<sub>2</sub>Cl<sub>2</sub> (100 ml) under argon was added 4-morpholinecarbonyl chloride (1.09 ml, 9.38 mmole) followed by NMM (0.52 ml, 4.69 mmole). After 105 minutes, the reaction mixture was concentrated to ca. 5 ml and loaded onto a column for chromatography. Flash chromatography (6.5 x 12 cm silica gel column), eluting with acetone/EtOAc (30:70), gave an oil. A mixture of ethyl ether and hexane was added and concentrated to give a white solid (0.78g). Elemental Analysis; calcd for C<sub>22</sub>H<sub>33</sub>F<sub>5</sub>N<sub>4</sub>O<sub>5</sub>: %C = 50.00, %H = 6.29, %N = 10.60. Found: %C = 49.88, %H = 6.59, %N = 10.62.

40 **EXAMPLE 2****Preparation of N-[4-(4-Morpholinylsulfonyl)benzoyl]-L-valyl-N-[3,3,4,4,4-pentafluoro-1-(1-methylethyl)-2-oxobutyl]-L-prolinamide**

45 To a solution of diisopropylethylamine (1.76 g, 13.6 mmol, 2.37 ml) and morpholine (1.98 g, 22.7 mmol, 1.98 ml) in THF (40 ml) was added, dropwise over 0.5 h, a solution of 4-(chlorosulfonyl)benzoic acid (2.50 g, 11.3 mmol) in THF (17 ml). After stirring at room temperature for 18 h the reaction was poured into H<sub>2</sub>O (150 ml) and washed with EtOAc. The aqueous layer was acidified (pH 1) with concentrated HCl, and the precipitate collected, washed with cold H<sub>2</sub>O, and dried under vacuum over P<sub>2</sub>O<sub>5</sub> to give 2.68 g (87%) of 4-(4-morpholinylsulfonyl)-benzoic acid as an off-white solid.

50 To a solution of the benzoic acid derivative prepared above (0.240 g, 0.885 mmol) and NMM (0.446 g, 4.43 mmol, 0.489 ml) in CH<sub>2</sub>Cl<sub>2</sub> (8.9 ml) at -22 °C under N<sub>2</sub> was added IBCF (0.121g, 0.885 mmol, 0.115 ml), and the reaction stirred at -22 °C for 20 min. The HCL·Val-Pro-Val-C<sub>2</sub>F<sub>5</sub> (0.400 g, 0.885 mmol) was added in several portions, and the reaction was stirred at -22 °C for 0.5 h, followed by 4 h at room temperature. The reaction was diluted with CH<sub>2</sub>Cl<sub>2</sub> (30 ml) and then washed successively with 10% HCl (2 x 15 ml), sat. NaHCO<sub>3</sub> (2 x 15 ml), brine (1 x 15 ml), and dried over MgSO<sub>4</sub>. Solvent removal under vacuum gave an off-white foam which was purified by flash chromatography (silica gel; 25/75, hexane/EtOAc) to give 0.295 g (50%) of the title compound as a white solid.

**EXAMPLE 3****Preparation of N-[2-(4-morpholinocarbonyl)-3-methylbutanoyl]-Val-Pro-Val-CF<sub>2</sub>CF<sub>3</sub>**5 a) Preparation of methyl 2-(4-morpholinocarbonyl)acetate

To a solution of methylmalonylchloride (10.0 g, 73.2 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (200 ml) at 0 °C under N<sub>2</sub> was added rapidly dropwise a solution of morpholine (16.0 g, 0.183 mmol, 16.0 ml) in CH<sub>2</sub>Cl<sub>2</sub> (50 ml), and the reaction stirred at room temperature for 4 h. The reaction was filtered, the filtrate diluted with additional  
 10 CH<sub>2</sub>Cl<sub>2</sub> (200 ml), and then washed successively with 10% HCl, sat. NaHCO<sub>3</sub>, brine, and dried over MgSO<sub>4</sub>. Solvent removal *in vacuo* gave a yellow oil which was purified by flash chromatography (silica gel, EtOAc) to give 9.70 g (71%) of the title compound, 1, as a pale yellow oil.

15 b) Preparation of methyl 2-(4-morpholinocarbonyl)-3-methylbutanoate

To a solution of the compound prepared in Example 3a (9.70 g, 51.8 mmol) in THF at 0 °C under N<sub>2</sub> was added NaH (1.71 g, 07.0 mmol, 80% dispersion in mineral oil) in three portions. After the initial reaction subsided the reaction was allowed to warm to room temperature, the isopropyl iodide (13.2 g, 77.7 mmol, 7.77 ml) added, and the reaction heated at 60 °C for 8 h followed by 64 h at room temperature. The  
 20 reaction was diluted with CH<sub>2</sub>Cl<sub>2</sub> (30 ml) and then washed with H<sub>2</sub>O, brine, and dried over MgSO<sub>4</sub>. Solvent removal *in vacuo* gave a brown oil which was purified by flash chromatography to yield 7.70 g (65%) of the title compound as an orange oil.

25 c) Preparation of 2-(4-morpholinocarbonyl)-3-methylbutanoic acid

To a solution of the compound prepared in Example 3b (7.70 g, 33.6 mmol) in MeOH (150 ml) was added LiOH (37 ml), 1 M in H<sub>2</sub>O and the reaction stirred at room temperature for 24 h. The reaction was acidified with conc. HCl and the solvent removed *in vacuo*. The residue was triturated with hexane, collected on a fritted funnel, washed with several portions of hexane, and dried *in vacuo* over P<sub>2</sub>O<sub>5</sub> to give  
 30 5.82 g (81%) of the title compound as a white solid.

d) Preparation of N-[2-(4-morpholinocarbonyl)-3-methylbutanoyl]-Val-Pro-Val-CF<sub>2</sub>CF<sub>3</sub>

To a suspension of the compound prepared in Example 3c (0.304 g, 1.33 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (8.9 ml) under N<sub>2</sub> was added N-methylmorpholine (0.446 g, 4.43 mmol, 0.489 ml), and the resulting clear, colorless  
 35 solution cooled to -22 °C. The IBCF (0.182 g, 1.33 mmol, 0.173 ml) was added and the reaction stirred for 20 min, followed by addition of the HCl\*Val-Pro-Val-CF<sub>2</sub>F<sub>3</sub> in one portion. After stirring at -22 °C for 4 h the reaction was diluted with additional CH<sub>2</sub>Cl<sub>2</sub> (35 ml) and washed successively with 10% HCl (3 x 20 ml), sat. NaHCO<sub>3</sub> (2 x 20 ml), brine (1 x 20 ml), and dried over MgSO<sub>4</sub>. Solvent removal *in vacuo* followed by  
 40 purification by flash chromatography (silica gel; 20/80, acetone/EtOAc) gave 0.343 g (63%) of the title compound as a white foam.

The foregoing describes in detail the generic and specific aspects of the scope of the invention as well as the manner of making and using the invention. In addition thereto, although such procedures are known in the art, references setting forth state of the art procedures by which the compounds may be evaluated for  
 45 their biochemical effects are also included herein.

By following the techniques referenced above, as well as by utilization of other known techniques, as well as by comparison with compounds known to be useful for treatment of the above-mentioned disease states, it is believed that adequate material is available to enable one of ordinary skill in the art to practice the invention. Of course, in the end-use application of the compounds of this invention, the compounds are  
 50 preferably formulated into suitable pharmaceutical preparations such as tablets, capsules or elixers, for oral administration or in sterile solutions or suspensions for parenteral administration. They can be administered to patients (animals and human) in need of such treatment in a dosage range of 5 to 500 mg per patient generally given several times, thus giving a total daily dose of from 5 to 2000 mg per day. As stated above, the dose will vary depending on severity of disease, weight of patient and other factors which a person  
 55 skilled in the art will recognize.

Typically the compounds described above are formulated into pharmaceutical compositions as discussed below.

About 10 to 500 mg of a compound or mixture of compounds of formula 1 or a physiologically acceptable salt is compounded with a physiologically acceptable vehicle, carrier, excipient, binder, preservative, stabilizer, flavor, etc., in a unit dosage form as called for by accepted pharmaceutical practice. The amount of active substance in these compositions or preparations is such that a suitable dosage in the range indicated is obtained.

Illustrative of the adjuvants which may be incorporated in tablets, capsules and the like are the following: a binder such as gum tragacanth, acacia, corn starch or gelatin; an excipient such as microcrystalline cellulose; a disintegrating agent such as corn starch, pregelatinized starch, alginic acid and the like; a lubricant such as magnesium stearate; a sweetening agent such as sucrose, lactose or saccharin; a flavoring agent such as peppermint, oil of wintergreen or cherry. When the dosage unit form is a capsule, it may contain in addition to materials of the above type, a liquid carrier such as fatty oil. Various other materials may be present as coatings or to otherwise modify the physical form of the dosage unit. For instance, tablets may be coated with shellac, sugar or both. A syrup or elixer may contain the active compound, sucrose as a sweetening agent, methyl and propyl parabens as preservatives, a dye and a flavoring such as cherry or orange flavor.

Sterile compositions for injection can be formulated according to conventional pharmaceutical practice by dissolving or suspending the active substance in a vehicle such as water for injection, a naturally occurring vegetable oil like sesame oil, coconut oil, peanut oil, cottonseed oil, etc., or a synthetic fatty vehicle like ethyl oleate or the like. Buffers, preservatives, antioxidants and the like can be incorporated as required. Pharmaceutical compositions containing the compounds of this invention can also be administered topically. This can be accomplished by simply preparing a solution of the compound to be administered, preferably using a solvent known to promote transdermal absorption such as ethanol or dimethyl sulfoxide (DMSO) with or without other excipients. Preferably topical administration will be accomplished using a patch either of the reservoir and porous membrane type or of a solid matrix variety.

Some suitable transdermal devices are described in U.S. Pat. Nos. 3,742,951, 3,797,494, 3,996,934, and 4,031,894. These devices generally contain a backing member which defines one of its face surfaces, an active agent permeable adhesive layer defining the other face surface and at least one reservoir containing the active agent interposed between the face surfaces. Alternatively, the active agent may be contained in a plurality of microcapsules distributed throughout the permeable adhesive layer. In either case, the active agent is delivered continuously from the reservoir or microcapsules through a membrane into the active agent permeable adhesive, which is in contact with the skin or mucosa of the recipient. If the active agent is absorbed through the skin, a controlled and predetermined flow of the active agent is administered to the recipient. In the case of microcapsules, the encapsulating agent may also function as the membrane.

In another device for transdermally administering the compounds in accordance with the present invention, the pharmaceutically active compound is contained in a matrix from which it is delivered in the desired gradual, constant and controlled rate. The matrix is permeable to the release of the compound through diffusion or microporous flow. The release is rate controlling. Such a system, which requires no membrane is described in U.S. Pat. No. 3,921,636. At least two types of release are possible in these systems. Release by diffusion occurs when the matrix is non-porous. The pharmaceutically effective compound dissolves in and diffuses through the matrix itself. Release by microporous flow occurs when the pharmaceutically effective compound is transported through a liquid phase in the pores of the matrix.

While the invention has been described in connection with specific embodiments thereof, it will be understood that it is capable of further modifications and this application is intended to cover any variations, uses, or adaptations of the invention following, in general, the principles of the invention and including such departures from the present disclosure as come within known or customary practice within the art to which the invention pertains and as may be applied to the essential features hereinbefore set forth, and as follows in the scope of the appended claims.

SEQUENCE LISTING

5

(1) GENERAL INFORMATION:

10

(i) APPLICANT: Peet, Norton p  
Angelastro, Michael R  
Burkhart, Joseph P

(ii) TITLE OF INVENTION: Novel Orally-Active Elastase Inhibitors

(iii) NUMBER OF SEQUENCES: 5

15

(iv) CORRESPONDENCE ADDRESS:

20

(A) ADDRESSEE: Marion Merrell Dow Inc.  
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(C) CITY: Cincinnati P. O. Box 156300  
(D) STATE: Ohio  
(E) COUNTRY: USA  
(F) ZIP: 45215-6300

25

(v) COMPUTER READABLE FORM:

(A) MEDIUM TYPE: Floppy disk  
(B) COMPUTER: IBM PC compatible  
(C) OPERATING SYSTEM: PC-DOS/MS-DOS  
(D) SOFTWARE: PatentIn Release #1.0, Version #1.25

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(vi) CURRENT APPLICATION DATA:

(A) APPLICATION NUMBER: US  
(B) FILING DATE:  
(C) CLASSIFICATION:

35

(vii) PRIOR APPLICATION DATA:

(A) APPLICATION NUMBER: US 07/748,607  
(B) FILING DATE: 22-AUG-1991

40

(viii) ATTORNEY/AGENT INFORMATION:

(A) NAME: Nesbitt, Stephen L.  
(B) REGISTRATION NUMBER: 28,981  
(C) REFERENCE/DOCKET NUMBER: M01627A US

45

(ix) TELECOMMUNICATION INFORMATION:

(A) TELEPHONE: (513) 948-7965  
(B) TELEFAX: (513) 948-7961  
(C) TELEX: 214320

50

(2) INFORMATION FOR SEQ ID NO:1:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 4 amino acids

55

(B) TYPE: amino acid  
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:1:

Xaa Xaa Xaa Xaa  
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(2) INFORMATION FOR SEQ ID NO:2:

(i) SEQUENCE CHARACTERISTICS:  
(A) LENGTH: 4 amino acids  
(B) TYPE: amino acid  
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(ix) FEATURE:

(A) NAME/KEY: Modified-site  
(B) LOCATION: 1  
(D) OTHER INFORMATION: /note= "morpholino carbonyl  
protected"

(ix) FEATURE:

(A) NAME/KEY: Modified-site  
(B) LOCATION: 4  
(D) OTHER INFORMATION: /note= "terminal OH is replaced by  
a perfluoroethyl group"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:2:

Ala Ala Pro Val  
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(2) INFORMATION FOR SEQ ID NO:3:

(i) SEQUENCE CHARACTERISTICS:  
(A) LENGTH: 4 amino acids  
(B) TYPE: amino acid  
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(ix) FEATURE:

(A) NAME/KEY: Modified-site

(B) LOCATION: 1  
 (D) OTHER INFORMATION: /note=  
 "4(morpholinocarbonyl)benzoyl protected"

5

(ix) FEATURE:  
 (A) NAME/KEY: Modified-site  
 (B) LOCATION: 4  
 (D) OTHER INFORMATION: /note= "terminal OH group replaced  
 by a perfluoroethyl group"

10

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:3:

Ala Ala Pro Val  
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15

(2) INFORMATION FOR SEQ ID NO:4:

(i) SEQUENCE CHARACTERISTICS:  
 (A) LENGTH: 4 amino acids  
 (B) TYPE: amino acid  
 (D) TOPOLOGY: linear

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(ii) MOLECULE TYPE: peptide

25

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:4:

Xaa Xaa Xaa Xaa  
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(2) INFORMATION FOR SEQ ID NO:5:

(i) SEQUENCE CHARACTERISTICS:  
 (A) LENGTH: 4 amino acids  
 (B) TYPE: amino acid  
 (D) TOPOLOGY: linear

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(ii) MOLECULE TYPE: peptide

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(xi) SEQUENCE DESCRIPTION: SEQ ID NO:5:

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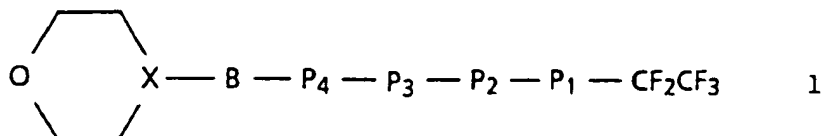
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# Claims

50 1. A compound of the formula

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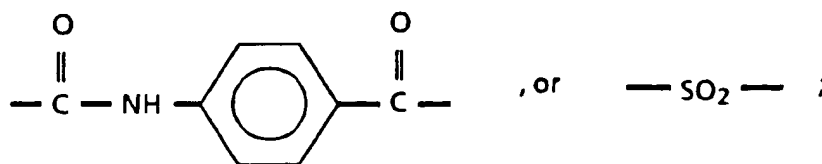
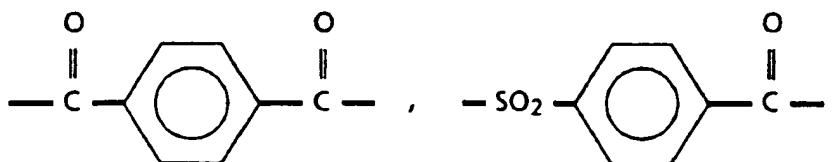
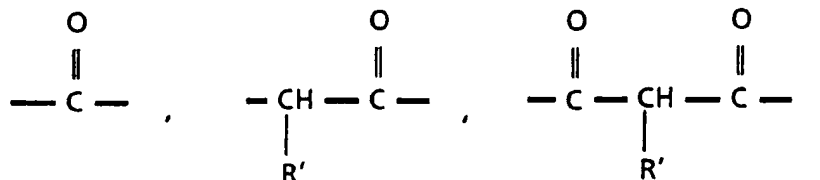




## SEQ. ID 1

wherein

- $\text{P}_1$  is Ala, bAla, Leu, Ile, Val, Nva, bVal, Met, Nle, Gly, or an N-methyl derivative;  
 $\text{P}_2$  is Ala, bAla, Leu, Ile, Val, Nva, bVal, Met, Nle, Gly, Phe, Tyr, Trp, or Nal(1) where the nitrogen of the alpha-amino group can be substituted with an R group where R is a (C<sub>1-6</sub>)alkyl, (C<sub>3-12</sub>)cycloalkyl, (C<sub>3-12</sub>)cycloalkyl(C<sub>1-6</sub>)alkyl, (C<sub>4-11</sub>)bicycloalkyl, (C<sub>4-11</sub>)bicycloalkyl(C<sub>1-6</sub>)alkyl, (C<sub>6-10</sub>)aryl, (C<sub>6-12</sub>)aryl(C<sub>1-6</sub>)alkyl, (C<sub>3-7</sub>)heterocycloalkyl, (C<sub>3-7</sub>)heterocycloalkyl-(C<sub>1-6</sub>)alkyl, (C<sub>5-9</sub>)heteroaryl, (C<sub>5-9</sub>)heteroaryl(C<sub>1-6</sub>)alkyl, fused (C<sub>6-10</sub>)aryl(C<sub>3-12</sub>)cycloalkyl, fused (C<sub>6-10</sub>)aryl(C<sub>3-12</sub>)cycloalkyl(C<sub>1-6</sub>)alkyl, fused (C<sub>5-9</sub>)heteroaryl(C<sub>3-12</sub>)cycloalkyl, or fused (C<sub>5-9</sub>)heteroaryl(C<sub>3-12</sub>)cycloalkyl(C<sub>1-6</sub>)alkyl, or  $\text{P}_2$  is Pro, Ind, 1,2,3,4-tetrahydro-3-isoquinoline carboxylic acid (Tic), thiazolidine-4-carboxylic acid (Tca), or Ind;  
 $\text{P}_3$  is Ala, bAla, Leu, Ile, Val, Nva, bVal, Met, or Nle or an N-methyl derivative, Pro, Ind, Tic or Tca, Lys or Orn each substituted on its omega amino group with a morpholino-B-group;  
 $\text{P}_4$  is Ala, bAla, Leu, Ile, Val, Nva, bVal, Met, or Nle or an N-methyl derivative or a bond; and  
 B is a group of the formulae



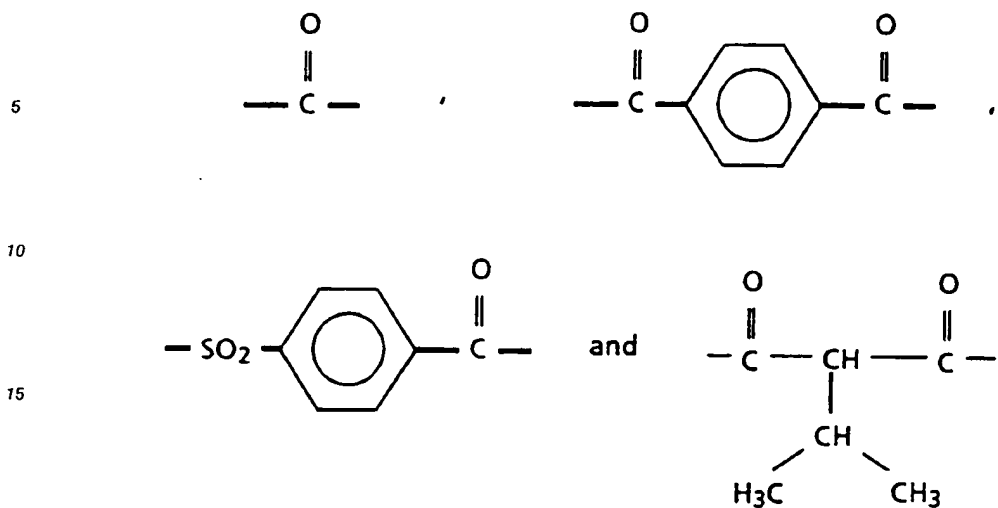
X is N or CH;

R' is hydrogen or a C<sub>1-6</sub>alkyl group;

or a hydrate, isostere, or pharmaceutically acceptable salt thereof.

2. A compound of claim 1 wherein

B is a group of one of the formulae

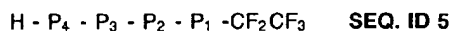


P<sub>1</sub> is norvaline or valine;  
P<sub>2</sub> is proline;  
P<sub>3</sub> is isoleucine, valine or alanine  
P<sub>4</sub> is alanine or a bond; and  
X is N.

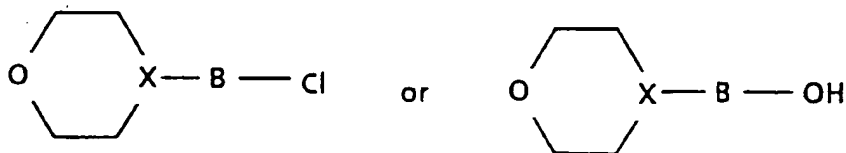
3. A compound of claim 1 selected from MC-Ala-Ala-Pro-Val-C<sub>2</sub>F<sub>5</sub> (SEQ. ID 2) and MC-Val-Pro-Val-C<sub>2</sub>F<sub>5</sub>, MCBz-Ala-Ala-Pro-Val-C<sub>2</sub>F<sub>5</sub> (SEQ. ID 3) and MCBz-Val-Pro-Val-C<sub>2</sub>F<sub>5</sub>.

4. A process for preparing a compound as defined in claim 1

which comprises reacting a pentafluoroethyl peptide derivative of the formula



with the appropriate compound of one of the formulae



wherein B is as defined above.

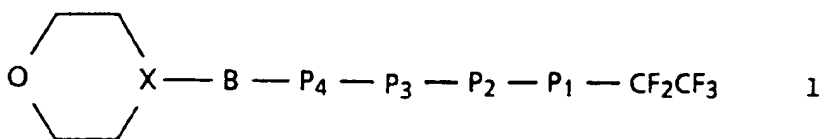
5. A pharmaceutical composition comprising a compound according to any one of claims 1 to 3.

6. Use of a compound according to any one of claims 1 to 3 for the preparation of a pharmaceutical composition useful in the treatment of an inflammatory disease.

7. Use of a compound according to any one of claims 1 to 3 for the preparation of a pharmaceutical composition useful in the treatment of emphysema.

Claims for the following Contracting States : ES, GR

1. A compound of the formula



SEQ. ID 1

15 wherein

$\text{P}_1$  is Ala, bAla, Leu, Ile, Val, Nva, bVal, Met, Nle, Gly, or an N-methyl derivative;

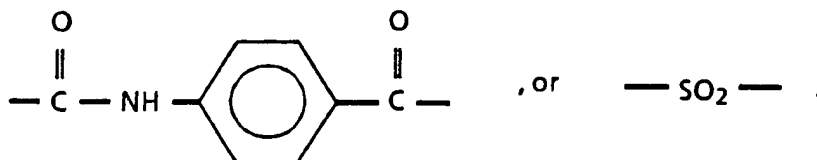
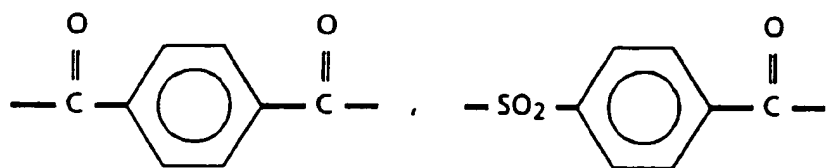
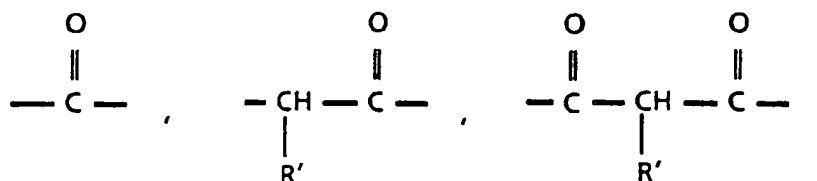
$\text{P}_2$  is Ala, bAla, Leu, Ile, Val, Nva, bVal, Met, Nle, Gly, Phe, Tyr, Trp, or Nal(1) where the nitrogen of the alpha-amino group can be substituted with an R group where R is a (C<sub>1-6</sub>)alkyl, (C<sub>3-12</sub>)cycloalkyl, (C<sub>3-12</sub>)cycloalkyl(C<sub>1-6</sub>)alkyl, (C<sub>4-11</sub>)bicycloalkyl, (C<sub>4-11</sub>)bicycloalkyl(C<sub>1-6</sub>)alkyl, (C<sub>6-10</sub>)aryl, (C<sub>6-10</sub>)aryl(C<sub>1-6</sub>)alkyl, (C<sub>3-7</sub>)heterocycloalkyl, (C<sub>3-7</sub>)heterocycloalkyl(C<sub>1-6</sub>)alkyl, (C<sub>5-9</sub>)heteroaryl, (C<sub>5-9</sub>)heteroaryl(C<sub>1-6</sub>)alkyl, fused (C<sub>6-10</sub>)aryl(C<sub>3-12</sub>)cycloalkyl, fused (C<sub>6-10</sub>)aryl(C<sub>3-12</sub>)cycloalkyl(C<sub>1-6</sub>)alkyl, fused (C<sub>5-9</sub>)heteroaryl(C<sub>3-12</sub>)cycloalkyl, or fused (C<sub>5-9</sub>)heteroaryl(C<sub>3-12</sub>)cycloalkyl(C<sub>1-6</sub>)alkyl, or  $\text{P}_2$  is Pro, Ind, 1,2,3,4-tetrahydro-3-isoquinoline carboxylic acid (Tic), thiazolidine-4-carboxylic acid (Tca), or Ind;

20

$\text{P}_3$  is Ala, bAla, Leu, Ile, Val, Nva, bVal, Met, or Nle or an N-methyl derivative, Pro, Ind, Tic or Tca, Lys or Orn each substituted on its omega amino group with a morpholino-B-group;

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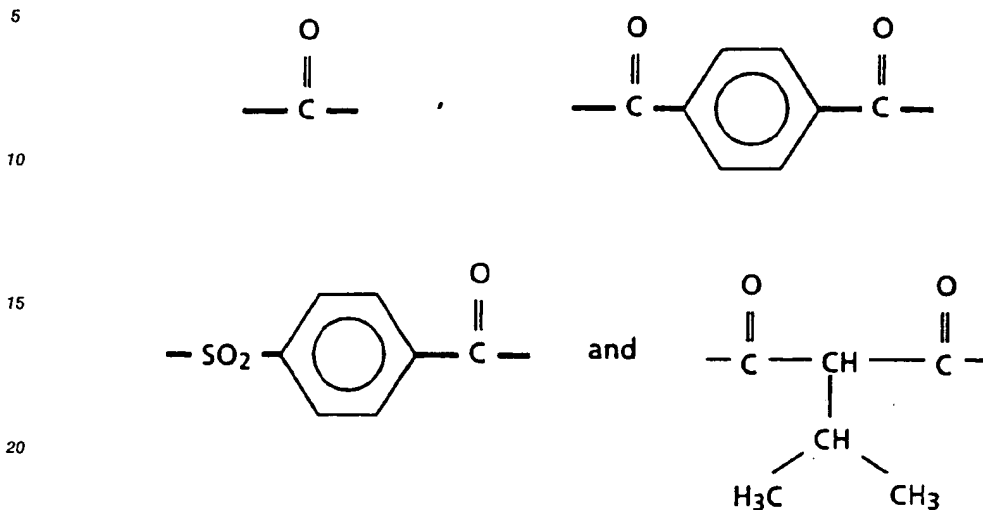
$\text{P}_4$  is Ala, bAla, Leu, Ile, Val, Nva, bVal, Met, or Nle or an N-methyl derivative or a bond; and  
B is a group of the formulae



X is N or CH;

55  $\text{R}'$  is hydrogen or a C<sub>1-6</sub>alkyl group;  
or a hydrate, isostere, or pharmaceutically acceptable salt thereof.

2. A compound of claim 1 wherein  
B is a group of one of the formulae

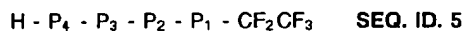


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- 30
- $P_1$  is norvaline or valine;  
 $P_2$  is proline;  
 $P_3$  is isoleucine, valine or alanine  
 $P_4$  is alanine or a bond; and  
X is N.

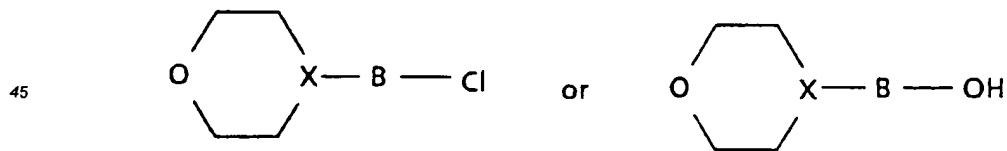
3. A compound of claim 1 selected from MC-Ala-Ala-Pro-Val- $\text{C}_2\text{F}_5$  (SEQ. ID 2) and MC-Val-Pro-Val- $\text{C}_2\text{F}_5$ , MCBz-Ala-Ala-Pro-Val- $\text{C}_2\text{F}_5$  (SEQ. ID 3) and MCBz-Val-Pro-Val- $\text{C}_2\text{F}_5$ .

4. A process for preparing a compound as defined in claim 1

35 which comprises reacting a pentafluoroethyl peptide derivative of the formula



40 with the appropriate compound of one of the formulae



50 wherein B is as defined above.

5. A method for the preparation of a pharmaceutical composition comprising combining a compound prepared according to any one of claims 1 to 3 with a pharmaceutically acceptable carrier.
- 55 6. A method according to claim 5 wherein the pharmaceutical composition prepared is useful in the treatment of an inflammatory disease.

7. A method according to claim 5 wherein the pharmaceutical composition prepared is useful in the treatment of emphysema.

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European Patent  
Office

## EUROPEAN SEARCH REPORT

Application Number

DOCUMENTS CONSIDERED TO BE RELEVANT			EP 92114411.9
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int. Cl.5)
P,X	WO - A - 91/13 904 (CEPHALON, INC.) * Page 56; claim 12 * --	1-3	C 07 K 5/08 C 07 K 5/10 C 07 K 1/00 A 61 K 37/02 A 61 K 37/64
P,X	WO - A - 91/15 487 (KOBAYASHI) * Abstract * --	1-3, 5-7	
A	EP - A - 0 318 318 (RADIOMETER CORP. DEVELOP. LTD.) * Abstract * --	1-3	
A	CHEMICAL ABSTRACTS, vol. 111, no. 9, August 28, 1989, Columbus, Ohio, USA LAFUMA, C. et al. "Lipo-peptides as bifunctional inhibitors; prevention of elastase-induced emphysema in mice by intratracheal pretreatment with oleoyl-alanyl-alanyl-prolyl-valine." page 17, column 1, abstract-no. 70 314q & Colloq. INSERM 1989, 174 (Forum Pept., 2nd, 1988) 321-4 --	1-7	
A	CHEMICAL ABSTRACTS, vol. 111, no. 21, November 20, 1989, Columbus, Ohio, USA GALZIGNA, LAURO et al. "A new synthetic peptide with elastase inhibiting effect." page 343, column 2, abstract-no. 190 131z & Biomed. Biochim. Acta 1989 48(8), 505-8 -----	1-7	
The present search report has been drawn up for all claims			
Place of search VIENNA		Date of completion of the search 19-11-1992	Examiner SCHARF
<b>CATEGORY OF CITED DOCUMENTS</b> X : particularly relevant if taken alone Y : particularly relevant if combined with another document of the same category A : technological background O : non-written disclosure P : intermediate document T : theory or principle underlying the invention E : earlier patent document, but published on, or after the filing date D : document cited in the application L : document cited for other reasons ----- & : member of the same patent family, corresponding document			